

## IRRITABLE BOWEL SYNDROME: PATHOPHYSIOLOGICAL AND PHARMACOLOGICAL ASPECTS AND USE OF OTILONIUM BROMIDE OR PINAVERIUM BROMIDE

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### Abstract

The Irritable bowel syndrome (IBS) is the most common gastrointestinal disorder worldwide with unclear etiology. It is considered a chronic, multifactorial, relapsing functional bowel disorder normally related to altered motility of gastrointestinal system and the mechanisms involved in its onset and progression are not clear. The abdominal discomfort or pain and modifications in bowel habit are not related to organic causes. Constipation, diarrhea, alternating diarrhea and constipation, mucus in stools, bloating, gas, dyspepsia, rectal pain are possible symptoms to IBS patients. Many clinical trials show positive effects in the main symptoms of IBS, showing that antispasmodics may regulate abdominal pain, distention, mucus in stool, stool consistency, and reduce defecation straining and urgency. Antispasmodics are the most common drugs used in the treatment of IBS and belong to a heterogeneous group of drugs that reduce smooth muscle contractility of the gut. These drugs are divided in agents that act directly on the calcium channels thus affecting intestinal smooth muscle and agents possessing anticholinergic/antimuscarinic activities. Otilonium and Pinaverium Bromide are related to the first group and many clinical trials with these agents show positive effects in the main symptoms of IBS, showing that these antispasmodics may regulate abdominal pain, distention, mucus in stool, stool consistency, and reduce defecation straining and urgency.

**Keywords:** Irritable bowel syndrome, otilonium, pinaverium bromide

## Introduction

The Irritable bowel syndrome (IBS) is the most common gastrointestinal disorder worldwide with unclear etiology. It is considered a chronic, multifactorial, relapsing functional bowel disorder normally related to altered motility of gastrointestinal system and the mechanisms involved in its onset and progression are not clear. The altered gastrointestinal motility is followed by alterations also in secretion and sensitivity reducing considerably quality of life of the patients and many evidences link inflammation and immune cells to the intestinal neuroendocrine system, which controls gastrointestinal sensory-motor function [1-6]. Three IBS clinical possibilities are recognized and they are based on the modification of bowel motility and the resulting predominant feature: diarrhea predominant IBS (D-IBS), constipation predominant IBS (C-IBS), and IBS with mixed features of diarrhea and constipation (M-IBS) [7].

In line with Rome III Diagnostic Criteria, IBS is a syndrome with recurrent abdominal pain or discomfort occurring at least 3 days per month over a 3 month span. It is related to two or more of the following patterns: defecation dysregulation, change in stool frequency with onset, and change in stool form with onset [8-9]. The abdominal discomfort or pain and modifications in bowel habit are not related to organic causes, constipation, diarrhea, alternating diarrhea and constipation, mucus in stools, bloating, gas, dyspepsia, rectal pain are possible symptoms to IBS patients (Figure 1) [10-13]. IBS prevalence is estimated around 10%-15% in United States and Europe. In the general population the prevalence ranges from 5 to 20% (in industrialized and non-industrialized countries). It is also known that women are more susceptible to IBS and symptoms are more severe when comparing to men and it is more common in younger adults (less than 50 years old). It can manifest before 35 years of age in 50 percent of patients. In adolescents it is related to anxiety and depression. Elderly population may also manifest symptoms but, new onset of symptoms after age 50 can be related to other organic causes. In general population the symptoms begin normally before 50 years of age [14-18, 12]. About 37% of IBS individuals have family history of the disorder and a recent study showed that the risk of IBS increase in the first-, second-, and third-degree relatives of IBS individuals when comparing to non-IBS counterparts. Besides, the risk seems to be higher in more closely related relatives. Also, studies in twins show a substantial genetic component in IBS and

about 60 gene candidates have been listed to play a role in the predisposition to this disorder [1, 19-20]. IBS is a very common disease although underdiagnosed and has deep impact in the patient quality of life. This review intended to point some pathophysiologic aspects of the disease, once they are barely understood, and compare the use of Pinaverium Bromide and Otilonium Bromide in the treatment of the main symptoms.

## Methods

The following databases were used: Pubmed, Medline, Scielo, Scopus and Lilacs in order to find relevant clinical trials or epidemiological studies and reviews limited to indexed scientific articles involving humans and animals.

## Pathophysiology of IBS

The pathophysiologic mechanisms involved in the IBS are possibly related to visceral hypersensitivity, psychological factors, neural immune endocrine imbalance, microbial high intestinal permeability, overgrowth, microinflammation, diet, infections, visceral hypersensitivity and genetics (Figure 2) [21-23]. The pathophysiological mechanisms involved in the IBS are not fully understood, but authors believe that this disorder may be consequence of dysregulation of the brain-gut with central and peripheral mechanism related. Central mechanisms are depression and anxiety and peripheral dysfunction are related to modifications in gut motility and secretion and visceral hypersensitivity. When cellular and molecular alterations occur in mucosal entero-endocrine system, mucosal and systemic immune responses have been associated to participate in the brain-gut dysfunction. The biochemical events observed involve a cascade of inflammatory process with the production of proinflammatory cytokines. These inflammatory processes include, for example, infectious gastroenteritis and idiopathic chronic inflammatory bowel diseases as Crohn's disease and ulcerative colitis. Nevertheless, the typical aspects of evident inflammation or mucosal alterations observed in these diseases are absent in IBS patients. In these individuals, there is a mild activation of the immune system locally in the intestinal mucosa and/or systemically (plasma and peripheral blood mononuclear cells) with an abnormal functional responses in enteric and sensory nerves and disruption in the intestinal barrier integrity. These effects may be directly associated with molecules of immune origin. Also, many current studies show increased levels of plasma pro-inflammatory

cytokines, as Interleucin-1 $\beta$  (IL-1 $\beta$ ), IL-6, IL-8, Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ), and increased synthesis of similar patterns of cytokines in IBS patients when compared with healthy ones. Also it is observed release of Th2 (T helper-2) cytokines, as IL-5 and IL-13 that normally are related to stimulation of immune activation seen in allergic disorders [12].

Other studies show an increase in the activated T-lymphocytes in mucosal from IBS patients and also in the blood. T lymphocytes are involved the activation of B lymphocytes and macrophages and the destruction of infected cells. Allied to this, higher expression of proinflammatory cytokines in peripheral blood mononuclear cells and serum is related to a predisposition to immune activation in IBS patients [8,24-25]. Figure 3 shows that factor related to the triggering of IBS are related to modifications in mucosal permeability and promotes an imbalance in the response to the microorganisms. This is related to macrophage activation as well B cell, T cell, Mast cell and APC cells (antigen presenting cells) with production of cytokines and IgA that are released in the blood [26]. IBS can be triggered by different factors that are related to the imbalance in the response to the microbiota and increase in the permeability of the intestinal epithelium resulting in an increase in the uptake of antigens. Toll like receptors (TLR) associated with activated dendritic cell and macrophages recognize commensal microbiota and are activated. This activation increases the production of proinflammatory cytokines as TNF- $\alpha$ , IFN- $\gamma$ , IL-1 $\beta$ , IL-6, IL-8, IL-12, IL-13 and the production of immunoglobulins. These substances are also increased in the plasma/serum of the IBS patients (TNF- $\alpha$ : Tumor Necrosis Factor- $\alpha$ ; IFN- $\gamma$ : Interferon- $\gamma$ , IL-1 $\beta$  (Interleucin-1 $\beta$ ), IL-6, IL-8, IL-12, IL-13) [26,27].

The low grade inflammation may be underlined as an increased infiltration in the colonic mucosa of T lymphocytes, mast cells and enteroendocrine cells. Studies have shown higher number of mast cells near to the colon sensory nerves are linked to the severity and frequency of abdominal pain, bloating and rectal hypersensitivity. Study previous related higher numbers of T and mast cells in about 50% of the IBS patients and found intermediate infiltration levels in IBS individuals comparing to controls, and lower levels when comparing to individual with Inflammatory Bowel Disease (Crohn's disease and ulcerative retocolitis) [28]. The authors postulate that inflammation may be a common factor triggering each these disorders, and IBS and IBD may be the two ends of a wide range of chronic

inflammatory conditions [26-27, 29-31].

### **Enteroendocrine system**

Enteroendocrine cells produce many bioactive compounds as gastrin, somatostatin, secretin, chromogranins, cholecystokinin and serotonin. When abnormalities in neuroendocrine peptides and amines from enteroendocrine cells are observed, it is possible to see disturbances in digestion, gastrointestinal motility and sensation in IBS individuals. One possibility to the occurrence of these abnormalities is gut luminal content, which contributes to the development of symptoms in IBS patients. The main type of these cells is called enterochromaffin cells that produce, store, and release serotonin in response to luminal stimuli. This molecule interferes in the motility, secretion and sensation in the gut through the stimulation of receptors from enteric nerves and sensory afferents. Studies demonstrated an alteration in the serotonin liberation in IBS. When there is increase in the production of this hormone, caused by luminal stimuli, there is activation of immune cells supporting the role that serotonin plays in the gut inflammation. Chromogranin and secretogranin also may interfere with gastrointestinal functions, as immune modulation and inflammation [8, 32-35].

Authors have reported increase of mast cell in the mucosa of IBS both in patients and in animal models with a possibly relationship with altered mucosal permeability. This imbalance in the mast cells leads to the release of tryptase, related to the development of a low grade inflammation, visceral hypersensitivity and high permeability. The influence of this enzyme in activating proinflammatory pathways stimulates the protease-activated receptor 2 (PAR-2). This receptor seems to be associated to visceral pain in the colon and elevation in the recruitment of inflammatory cells and to hypersensitivity symptoms due to a neurogenic mechanism related to afferent neurons and production of the calcitonin gene-related peptide and substance. These two neuropeptides associated with another one called vasoactive intestinal peptide play important role in regulation of visceral sensation and gastrointestinal motility [3, 36-39].

### **Pharmacological approach**

There are a number of pharmacological targets possibilities for alleviating IBS symptoms, but only a few have been implemented. This means that there is an urgent need of a multidisciplinary approach for IBS prevention, treatment and maintenance of remission due to the complex pathogenesis,

difficulties in defining the diagnosis and many forms or manifestation of the disease. Drugs commonly used are antispasmodics, antibiotics, antidiarrheal, prokinetics, antipruritics, antidepressants, but the most common are the antispasmodics [4, 40-41].

#### ***Use of antispasmodics***

Antispasmodics belong to a heterogeneous group of drugs and act in order to reduce smooth muscle contractility of the gut. Based on the mechanism of action these drugs may be divided into A) agents that act directly on the calcium channels thus affecting intestinal smooth muscle. In this group it is possible to include pinaverium bromide, otilonium bromide, alverine citrate, peppermint oil, and mebeverine) and B) agents possessing anticholinergic/antimuscarinic activities. In this group it is possible to add butylscopolamine, hyoscine, pirenzepine, dicyclomine, cimetropium and prifinium bromide [40, 42]. Anticholinergics agents may decrease the intestinal motility and secretion because of the blockade of the receptor of acetylcholine to its receptor. These drugs may display other roles in other body organs due to the muscarinic receptors, resulting in side effects such as impaired vision, dry mouth, and tachycardia [43-44]. The other group of agents acts on the calcium channels and results in slow colonic transit, as well as in the improvement of stool consistency and frequency, and normally do not exhibit the side effects as the anticholinergic agents [40-43].

#### ***Use of Otilonium Bromide***

Otilonium Bromide (OB) is a quaternary ammonium derivative. Due to this kind of structure, it results in minimal systemic absorption from the gastrointestinal, thus, it is almost completely excreted in the feces. It exhibits a selective antispasmodic effect on the gastrointestinal tract, mainly in the colon. OB effects are rather complex but mainly it has the capacity to block L-type calcium-channels, but binding to muscarinic M1, M2, M4 and M5 receptors. When there is antagonism of M3-coupled calcium signals in human colonic crypt cells may result in an anti-secretory action in IBS-D patients. It may also bind to tachykinin NK2 receptors. As a result of this dual effect, it may act as spasmolytic as well as anti-secretory agent. It may also reduce the peripheral sensory afferent transmission to the central nervous system by antagonism of tachykinin NK2 receptors. Due to these mechanisms of action authors have suggested that OB may be effective in the treatment of IBS-D symptoms by promoting

reduction of hypermotility and hypersensitivity. Studies show that its use may significantly improve symptoms of diarrhea and abdominal pain. By the other hand, it is possible to observe the occurrence of adverse effects as dry mouth, nausea, and dizziness [40, 45-48]. Because of the antagonism of tachykinin NK-2 receptors, OB do not only causes spasmolysis but also minimizes peripheral sensory afferent transmission to the central nervous system which could be effective in reducing spasms and abdominal pain that are the main symptoms of IBS. Further, OB may exert inhibitory effects on primary sensory afferents, resulting in reducing hypersensitivity, which is a common in IBS patients [42,49]. Table 1 shows some studies using this drug in the treatment of IBS.

#### ***Use of Pinaverium Bromide***

As OB, Pinaverium Bromide (PB) is a also quaternary ammonium derivative and is poorly absorbed from the gastrointestinal tract and its mainly pharmacological effects are in this region. This drug is also related to the reduction of abdominal pain and stool frequency [40, 57].

Authors have been shown that its effects are much similar to those of the established L-type calcium-channel blockers; reducing the plateau phase of slow waves, thereby inhibiting calcium influx and preventing contractions. It also may inhibit the contractile response in rat colonic smooth muscle preparations to acetylcholine and inhibits contraction in colonic smooth muscle cells isolated from normal or inflamed human colons. PB effects are more evident in inflamed colonic cells and its action is mediated by the inhibition of calcium influx through L-type calcium channels. PB also suppresses the hyper motility observed in animal models after induced stress what supports its indication to IBS patients. Also in animal model, this drug may inhibit increases in colonic spike burst frequency in animals chronically using an intraparietal electrode in the proximal colon. Initial clinical responses to PB in abdominal pain, diarrhea, and distention, ranged from three to six days and complete response may be obtained with four weeks what make author suggest at least four weeks to evaluate the therapeutic response. Table 1 shows some studies using this drug in the treatment of IBS [42, 58-60]. The authors evaluated the effectiveness and safety of PB in a double-blind, placebo-controlled trial and the results are summarized in Table 2 [41]. In this study, only a few patients related side effects as nausea, dizziness, increased blood pressure, and abdominal discomfort.

Authors concluded that PB can be considered a first-line treatment for IBS. Table 3 shows a comparison between some aspects of the effects of OB and PB. Antispasmodics such as Otilonium Bromide and Pinaverium Bromide are poorly absorbed in the gastrointestinal tract, thus without cardiovascular actions and with a few side effects. On account of this, they are widely used in the therapeutic approach for IBS patients. Their main actions are based on the spasmolytic properties by calcium influx inhibition into smooth muscle cells. Many clinical trials show positive effects in the main symptoms of IBS, showing that these antispasmodics may regulate abdominal pain, distention, mucus in stool, stool consistency, and reduce defecation straining and urgency.

### Conflict of interests

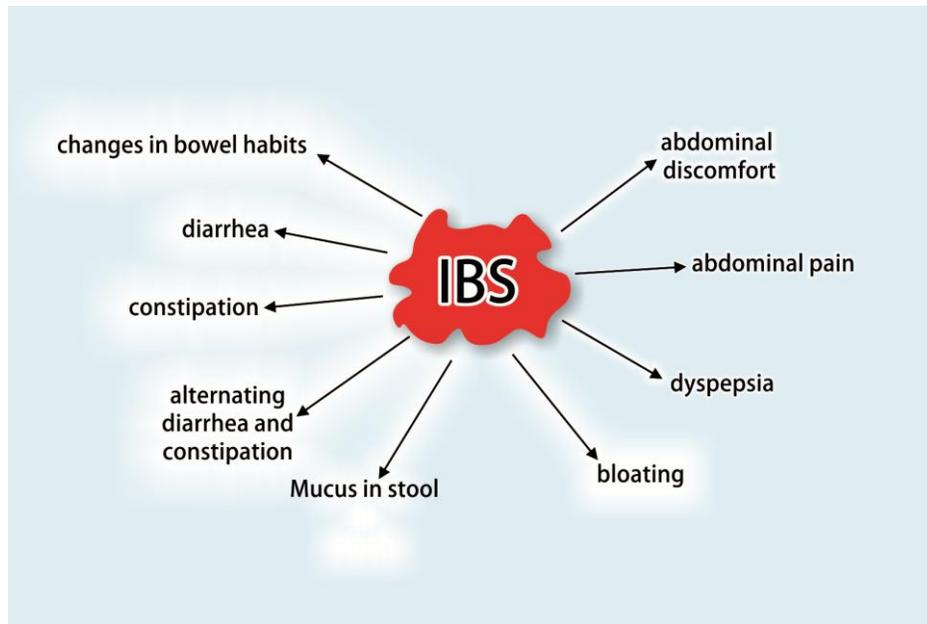
Authors declare no financial support or another conflict of interests.

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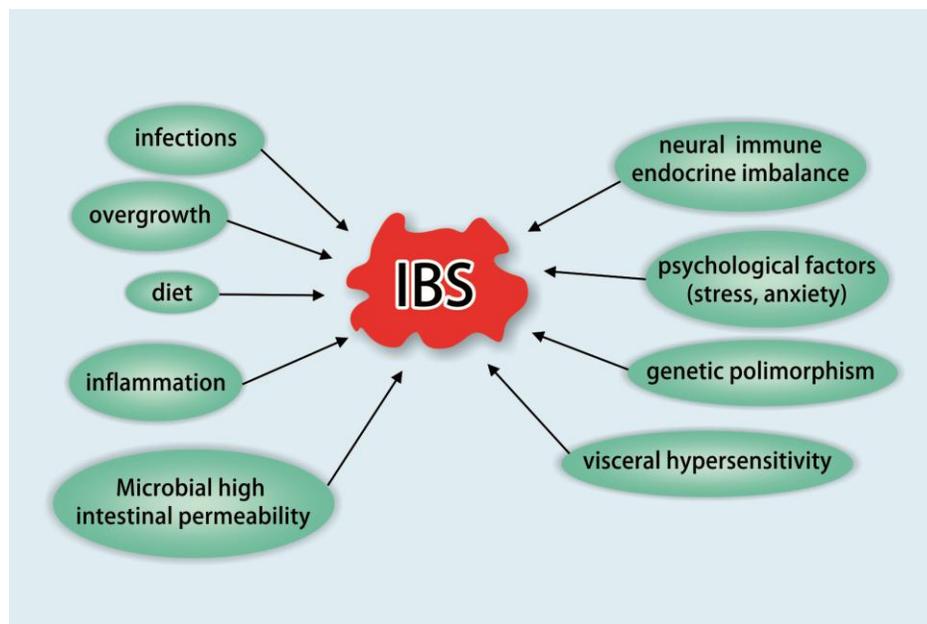
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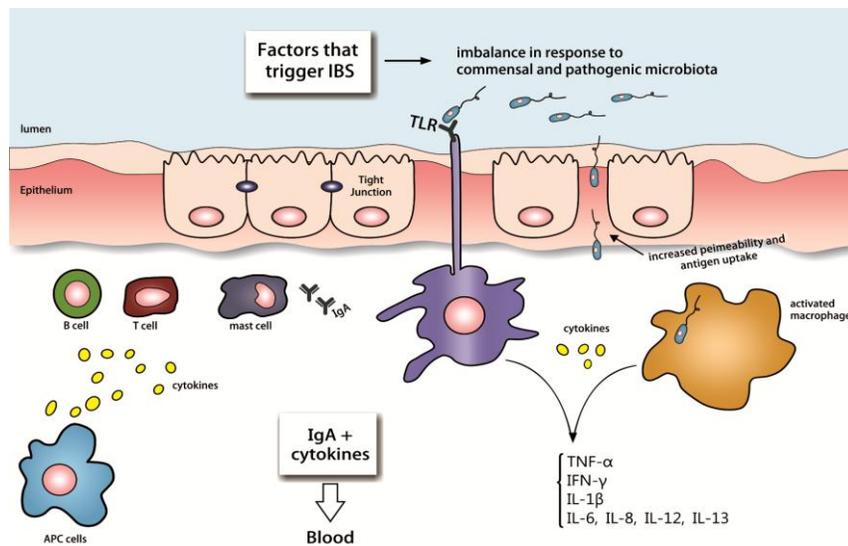
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**Figure 1.** Symptoms that may be found in IBS patients.



**Figure 2.** Mechanisms involved in the IBS.



**Figure 3.** Pathophysiological mechanisms involved in the Irritable Bowel Syndrome. Modified from Ordas et al. [27]; Rodrigues-Fandino et al. [26] and Ohman et al. [24].

**Table 1.** Use of Otilonium Bromide in the treatment of Irritable Bowel Disease (outcomes of randomized, double-blind, placebo controlled clinical trials and reviews).

| Patients (n) and doses         | Effects                                                                                                                                                                                                                                                                                                                                        | Reference |
|--------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| 72 patients/40mg, 3 twice/day  | Significant reduction on sigmoid motility; no significant difference in abdominal pain, and general well-being comparing to placebo                                                                                                                                                                                                            | [50, 51]  |
| 325 patients/40mg, 3 twice/day | significant reduction in abdominal pain, and frequency, reduced tenderness of the sigmoid colon, higher general well-being; improvement in number of evacuations and severity of diarrhea/constipation; more effective in treating diarrhea, but not constipation                                                                              | [52]      |
| 72 patients/40mg, 3 twice/day  | Reduction in abdominal pain, frequency and discomfort Improvement in the defecation disturbances occurred similarly in both groups                                                                                                                                                                                                             | [53]      |
| 378 patients/40mg, 3 twice/day | Reduction in abdominal pain, frequency and bloating and improvement stool frequency and general well-being compared to placebo; reduced symptom recurrence after treatment.                                                                                                                                                                    | [54]      |
| Review                         | Improvement in the severity of abdominal pain frequency and bloating, stool frequency, consistency or mucus in the stool and well-being compared to placebo; dramatically reduction in abdominal pain frequency from more than half of the days to less than one day per week, (while observing persistent 1-3 episodes in the placebo group). | [55]      |
| Review                         | Reduction in abdominal pain and discomfort. Long-term treatment may be safe and effective to most patients with IBS                                                                                                                                                                                                                            | [56]      |

**Table 2.** Use of Pinaverium Bromide in the treatment of Irritable Bowel Disease (outcomes of randomized, double-blind, placebo controlled clinical trials).

| Patients (n) and / or doses                                         | Effects                                                                                                                                                                                                            | Reference |
|---------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| 50mg/3twice/day                                                     | Significant reduction on the post-prandial rectal spike amplitude compared to placebo                                                                                                                              | [61]      |
| 12patients/50mg/<br>3twice/day                                      | Improvement in abdominal pain, bloating and altered bowel habits.                                                                                                                                                  | [62]      |
| 36 patients/100mg/<br>2twice/day                                    | Improvement in diarrhea / constipation, abdominal pain and distension.                                                                                                                                             | [63]      |
| 662 patients/ 100mg/2twice/day                                      | Improvement in diarrhea/constipation, abdominal pain (in 92% of the patients) and intestinal motility.                                                                                                             | [64]      |
| 12patients/50mg/<br>3twice/day                                      | Increase in fasting and postprandial colonic motility parameters compared to controls; improvement in abdominal pain, bloating, and stool frequency was normalized in both diarrheic and constipated IBS patients. | [65]      |
| 61patients                                                          | Significant reduction in abdominal pain, mucus in stool; improvement of stool consistency; reduce in the defecation straining and urgency, few side effects.                                                       | [66]      |
| 1677 patients/100 mg<br>pinaverium+300 mg<br>simethicone/2twice/day | Improvement in stool frequency and consistency in C-IBS, D-IBS and M-IBS patients; significant reduction of intensity of abdominal pain and bloating.                                                              | [67]      |
| 128 patients (and 208 placebo)/ 50<br>mg/ 3 twice/day               | Reductions in abdominal pain and Bristol stool score and secondary they observed reduction in pain and stool frequencies and abdominal discomfort and frequency.                                                   | [41]      |

D-IBS: diarrhea predominant-Irritable Bowel Disease; C-IBS: constipation predominant-Irritable Bowel Disease; M-IBS: mixed constipation/diarrhea Irritable Bowel Disease.

**Table 3.** Comparison between Otilonium Bromide and Pinaverium Bromide in some aspects of the Irritable Bowel Disease and the mains side effects.

| General aspects     | Otilonium Bromide                                                | Pinaverium Bromide                                           |
|---------------------|------------------------------------------------------------------|--------------------------------------------------------------|
| Mechanism of Action | voltage-gated calcium channels regulation                        | voltage-gated calcium channels regulation                    |
| Abdominal Pain      | ++                                                               | ++                                                           |
| Stool Frequency     | +                                                                | ++                                                           |
| Constipation        | +                                                                | ++                                                           |
| Diarrhea            | +                                                                | ++                                                           |
| Distention          | +                                                                | ++                                                           |
| Adverse effects     | dry mouth, nausea, constipation, diarrhea, dizziness, distention | headache, tachycardia vomiting, nausea, abdominal discomfort |
| Authors             | [40, 46-47]                                                      | [40-41]                                                      |

+, ++: efficacy of the treatment